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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,913	BIRKETT, ASHLEY J.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101-109 and 116-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101-109 and 116-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the Patent and Trademark Office has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Bo Peng, Art Unit 1648.

2. This Office Action is in response to the amendment filed 1 April 2005. Claims 1-97 and 110-115 have been cancelled by preliminary amendment. Claims 98-100 are cancelled and new claims 116-118 are added. Accordingly, claims 101-109 and 116-118 are pending, and are under consideration.

3. The rejection of claims 79-97 and 110-115 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, **is withdrawn** in view of Applicant's amendment and arguments.

4. The rejection of claims 98-100 under 35 U.S.C. § 112, first paragraph for lacking enablement, **is withdrawn** in view of the amendment. The rejection of claims 101-109 under 35 U.S.C. § 112, first paragraph for lacking enablement, **is maintained** and extended to new claims 116-118.

5. Claims 101-118 are directed to a nucleic acid encodes a recombinant HBc protein chimer molecule or a variant, analog or complement thereof. The specification on page 55 defines a variant, analog or complement recited as follows:

A nucleic acid sequence (DNA sequence or an RNA sequence) that (1) itself encodes, or its complement encodes, a chimer molecule whose HBc portion from residue position 1 through 136, when present, is that of SEQ ID NOs: 246, 247, 248, 249, 250 or 251 and (2) hybridizes with a DNA sequence of SEQ ID NOs: 274, 275, 276, 277, 278 or 279 at least at moderate stringency (discussed above); and (3) whose HBc sequence shares at least 80 percent, and more preferably at least 90 percent, and even more preferably at least 95 percent, and most preferably 100 percent identity with a DNA sequence of SEQ ID NOs: 274, 275, 276, 277, 278 and 279, is defined as a DNA variant sequence.

An analog or analogous nucleic acid (DNA or RNA) sequence that encodes a contemplated chimer molecule is also contemplated as part of this invention. A chimer analog nucleic acid sequence or its complementary nucleic acid sequence encodes a HBc amino acid residue sequence that is at least 80 percent, and more preferably at least 90 percent, and most preferably is at least 95 percent identical to the HBc sequence portion from residue position 1 through residue position 136 shown in SEQ ID NOs: 246, 247, 248, 249, 250 and 251. This DNA or RNA is referred to herein as an "analog of" or "analogous to" a sequence of a nucleic acid of SEQ ID NOs: 274, 275, 276, 277, 278 and 279, and hybridizes with the nucleic acid sequence of SEQ ID NOs: 274, 275, 276, 277, 278 and 279 or their complements herein under moderate stringency hybridization conditions.

6. According to the specification, the structural limitations of the claims 116-118 clearly covers very broad HBc variants, analogs or complements with undefined sequences as long as they hybridize with a DNA sequence of SEQ ID NOs: 274, 275, 276, 277, 278 or 279 at moderate stringency and encode a peptides having 80% similarity to HBc. The possible variations are enormous for such HBc variants, analogs and complements.

7. Since HBc variants differ in their sequences and structural requirements for their capsid formation, one skilled in the art would need specific directions on how to manipulate HBc variants having 80% similarity to HBc to display epitopes and also form stable particles. The specification, however, fails to provide these directions for undefined HBc variants. Based on the lack of guidance and working examples and unpredictable nature of the art, one skilled in the art would have to do an **undue** amount of experimentation to test large amounts of variants, analogs or complements with undefined sequences encompassed by the claims to see if they meet the function limitation of the claims to form stable virus like particles. Therefore, the instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

8. The rejection of claims 98-101, 103-105, 108 and 109 under 35 U.S.C 102(b) as being anticipated by Zlotnick (1997) **is withdrawn** in view of Applicant's amendment. The rejection of claims 102, 106 and 107 under 35 U.S.C 102(b) as being anticipated by Zlotnick, **is maintained**, and now extended to new claim 117.

9. Applicant argues that Zlotnick's constructs do not contain an inserted peptide-bond epitope sequence. In response to this argument, instant claims 102, 106, 107 and 117 do not require an epitope sequence in the recombinant HBc, or a variant, analog or complement thereof, as evidenced by claim 117(a) recited: "optionally includes a heterologous epitope" and by claim 117 b(ii) recited: "or the sequence of HBc at positions 76 to 85 is present free from heterologous residues". Moreover, all Zlonick's constructs contain a nucleic acid sequences that encode peptides have more than 80% similarity to HBc. Thus they are HBc variants accoding to the definition of a variant in the instant specification (p. 55, and recited above). Thus Zlotnick's constructs meet the structural limitation of claim 117. As a result, claims 102, 106, 107 and 117 are anticipated by Zlotnick.

10. The rejection of claims 98-109 under 35 U.S.C 102(b) as being anticipated by Yoshikawa (1993) **is withdrawn** in view of Applicant's amendment.

11. The rejection of claims 98-100 under 35 U.S.C. 103(a), as being unpatentable over Pumpens et al. (1995) in view of Zlotnick et al (1997), **is withdrawn** in view of Applicant's amendment. The rejection of claims 100-109 under 35 U.S.C. 103(a), as being unpatentable over

Pumpens et al. in view of Zlotnick et al, **is maintained**, and now extended to new claims 115-118.

12. Applicant argues that the rejection should be withdrawn because (1) Pumpens' statement that foreign insertions exert a stabilizing effect on chimeric HBcΔ is not persusive because it is based on unpublished results; and (2) Zlotnick's reference does not apply to the instant claims because it says nothing about the effect of a C-terminal cysteine on a truncated HBc molecule that has its internal cysteines nor such a molecule that has an inserted sequence.

13. Applicant's arguments have been considered but are found not persuasive for the following reasons:

14. Applicant's argument (1) that Pumpens' statement that foreign insertions exert a stabilizing effect on chimeric HBcΔ lacks legitimacy because it is based on unpublished results is not convincing because Pumpens' statement is published as a written record. Any published statements, suggestions, opinion, written records, etc. reflect the state of the prior art and knowledge of one of skill in the art, and can be used for assessing the obviousness of an invention at the time the invention is made.

15. In response to applicant's argument (2), Zlotnick's study is related to HBV assembly, which has provided general knowledge that would lead one of ordinary skill in the art to combine the relevant teachings of the references. Specifically, Zlotnick has studied the encapsidation and organization of a HBV pregenome by investigating the determinant of HBV capsid assembly. Zlotnick teaches that the protamine domain (residues 150-183) is required for packaging RNA and that deletion of this region results in the generation of virus capsids free of RNA and that deletion of this region results in the generation of virus capsids free of RNA encapsidation

(abstract; pg. 9556, col.1; pg. 9560, col. 2).

16. Zlotnick also teaches that the addition of a single heterologous Cys at a truncated C-terminal of HBV can stabilize the virus capsid after deletion of its protamine domain 150-183. (See Capsids assembled from Cpg. 9558, col. 6). To illustrate this, Zlotnick has created constructs Cp*149 and Cp*150 which contain HBc having a deleted C-terminal. He has replaced three native internal Cys by three Ala in the constructs Cp*149 and Cp*150, since Ala is a simplest amino acid residue and has minimal effect on the formation of higher protein structure. In addition, Zlotnick has introduced a single heterologous Cys at the truncated C-terminal of Cp*150. Zlotnick has shown that the Cp*150 construct that contained no internal Cys and had a C-terminal Cys is more stable than the Cys-free construct Cp*149, suggesting that disulfide bond formation by Cp*150 can promote capsid assemble (Results and Discussion, paragraph 1 and 2, p. 9558).

17. Thus, Zlotnick has provided the knowledge of minimal determinant of HBV capsid assembly, which is important for the art of basic and applied HBV virology, because "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In the instant case, one of ordinary skill in the art would apply this general knowledge of HBV assembly to the construction of HBc chimer.

18. As discussed in the previous Office action, it is known in art that one of the potential problems with full-length HBc core protein molecules is that the C-terminal sequence, including the protamine region, is responsible for the packaging of nucleic acid, and, moreover, when one

includes this region in a chimera one runs the risk of inadvertent transfer of endogenous nucleic acid from the host cell (See Ulrich, et al., 1998, pg. 163; cited by applicant as A108). Deletion of protamine domain results in virus capsids free of RNA encapsidation (abstract; pg. 9556, col.1; pg. 9560, col. 2).

19. One of ordinary skill in the art would have been motivated to combine the teachings of Pumpens outlining the various uses of HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimera, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability.

20. One of ordinary skill in the art would have expected achieve a more stable HBc chimera with a c-terminal truncation by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

21. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. The Applicant has not provided any compelling reason or evidence to overcome the rejection under 35 U.S.C. §103.

22. The provisional rejection s of claims 98-109 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-46 of copending Application No. 10/732,862, **are withdrawn** in view of the approval of Applicant's Terminal Disclaimer.

23. Followings are new grounds of rejection:

Claim Rejections - 35 USC § 112, second paragraph

24. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. Claim 116 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

26. Claim 116 (b) is indefinite because "from the C-terminal residue of HBc sequence" does not define what the specific position or residue of HBc the claim refer to since C-terminal of HBc is a region of amino acids. Moreover, this limitation does not necessarily agree with the next limitation recited: "**and** within about 30 residues from the C-terminus of the chimer molecule, because the length of a chimer molecule varies, so is its C-terminus. Thus one would not know what the structural requirement of claim 116(b) is. Finally, it is not clear what [C-terminal cysteine residue (s)] means? Is the context inside bracket deleted? If so, it is not consistent with strikethrough.

Remarks

27. No claims are allowed.

28. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Other issues

29. Regarding if a petition is needed to correct priority claim, no petition is needed in view of Applicant's explanation. Applicant, however, should submit a corrected application data sheet to correct domestic priority information.

30. Receipt is acknowledged of papers about Inventionship issue submitted by Applicant, which papers have been placed of record in the file.

31. The information disclosure statement submitted on April 1, 2005 is in compliance with

the provisions of 37 CRF 1.97. Accordingly, the information disclosure statement has been considered by Examiner. An initialed and dated copy of Applicant's IDS form 1449 is attached to the instant Office action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Bo Peng, Ph.D.
June 14, 2006

JEFFREY STUCKER
PRIMARY EXAMINER